Comment on "Chronic Alcohol Consumption Increases the Severity of Murine Influenza Virus Infections"

Jiezhong Chen

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read the paper entitled “Chronic alcohol consumption increases the severity of murine influenza virus infections” by Meyerholz and colleagues (1). The authors demonstrated an important fact that chronic alcoholic consumption increased influenza severity. To answer why this happened, they focused on a decrease in CD8+ T cells, which was considered to be the main reason. The result is consistent with the finding that mice lacking CD8+ T cells have increased viral replication and morbidity after infection with influenza PR8 virus (2). However, host response to influenza virus infection is a complicated system that includes an intact and functional cascade of changes; each element may play an important role. CD8+ T cells are probably one of many elements of host immune responses decreased by ethanol. These responses include innate immunity (cytokine and IFN production, macrophage function, dendritic cells, and NK cell function) and adaptive immunity (cytotoxic T lymphocyte activity as well as influenza-specific IgM and IgG antibodies). It has been shown that defects in IFN-α and -β lead to increased morbidity and mortality in mice (3, 4). Influenza virus produces NP protein to inhibit IFN-β, indicating its importance in the immune response against influenza (5). NK cells and macrophages are very early responders and have also been demonstrated to be critical for host survival of the infection (6). Plasmacytoid dendritic cells present virus Ag to CD8+ T cells through MHCI and is also important for host immune responses (7). CD4+ and CD8+ T cells and B cells act together; each one alone is not sufficient to overcome virus. For example, CD4+ T cells can help B cells to produce Ab (8). Both activation of CD4+ and CD8 need their costimulators, OX40 and 4-1BBL, respectively (9). Thus, they work in combination to fight virus and single element defect could be compensated by others. It is also important to examine other immune responses, especially Ab production, which appears as early as day 7; they are critical for control of influenza as published recently (10). Indeed, other studies showed that ethanol can inhibit TNF (11, 12), NK cells (13), and IFNγ (14). It also decreases IL-12 and increases IL-10 to cause immune suppression (15).

Jiezhong Chen

John Curtin School of Medical Research
Australian National University
Canberra, Australia

References

Response to Comment on “Chronic Alcohol Consumption Increases the Severity of Murine Influenza Virus Infections”

We fully agree with Dr. Chen that immunity to primary influenza virus challenge and ultimately clearance of the virus and resolution of the infection is complex and multifactorial. These factors include but are not limited to the adaptive arm of the immune response including CD8+ T cells, CD4+ T cells, and B cells as well as innate cells such as NK cells, dendritic cells, macrophages, etc., and even the infected respiratory epithelium and airway surface fluid (1–4). The purpose of our study was to illustrate the destructive impact of chronic alcohol consumption on pulmonary influenza
of the pulmonary inflammatory response. Importantly, we focused on the analysis of pulmonary epithelial integrity and dysregulation and humoral immunity after influenza challenge in chronic alcoholic animals (6). Although innate and other adaptive immune factors are able to control primary infections in the absence of CD8 T cells when less virulent influenza virus strains are used (7), they were unable to adequately control the A/PR/8/34 infection and protect against mortality in this study. To what extent these other antiviral innate and adaptive mechanisms are compromised by chronic alcohol consumption is a key question, and we agree with Dr. Chen that they also need to be explored. Toward this end, ongoing work at the University of Iowa using the same alcohol consumption model has demonstrated the integrity and function of the B cell compartment to be intact at 4 and 8 wk, the time points used in this study, although humoral immunity is diminished with extended periods of ingestion (24–32 wk; T. Waldschmidt, personal communication). Further studies have shown 4 and 8 wk of ethanol intake to alter the activation state of CD8 T cells, increase CD4:CD8 T cell ratios, reduce the numbers of dendritic cells, and alter dendritic cell function and/or migration from peripheral sites (8–10). The negative effect of alcohol consumption on CD8 T cell function highlighted in the paper, as well as significant alterations in dendritic cells, macrophages and inflammatory cytokines (described in Discussion) are consistent with these findings. The detailed examination of innate, CD4 T cell, and humoral immunity after influenza challenge in chronic alcohol mice is part of an active program in the laboratory, as is the analysis of pulmonary epithelial integrity and dysregulation of the pulmonary inflammatory response. Importantly, we share Dr. Chen’s goal of fully understanding the extent of damage that long-term ethanol intake has on the lung environment and pulmonary immune response.


*Department of Pathology
†Interdisciplinary Graduate Program in Immunology
University of Iowa
Iowa City, IA 52240

References